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Case Report

Recovery from Fulminant Hepatic Failure and Prolonged Deep Coma without Liver Transplantation

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The overall mortality of fulminant hepatic failure without liver transplantation is around 70%. However, the most critical problem in the management of fulminant hepatic failure is the indication of liver transplantation because this disease is sometimes reversible without such treatment. We encountered a 27-year old patient with acute type fulminant hepatic failure and deep coma (grade V hepatic encephalopathy). Electroencephalography showed generalized low voltage activity in all leads, but cranial computed tomography revealed no diffuse brain edema. The patient was treated with artificial liver support without liver transplantation, and finally recovered without any neurological deficits. The indications for liver transplantation in patients with deep coma are still controversial because the reversibility of severe coma cannot be accurately predicted before the transplantation. Therefore, more data are needed for the correct therapeutic management (with or without liver transplantation) of fulminant hepatic failure.

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Introduction

In Japan, fulminant hepatitis is used as a partial synonym for fulminant hepatic failure, and is applied to patients in whom grade $\geq$ II of hepatic encephalopathy occurs within 8 weeks from the first symptoms of hepatitis, with a prothrombin time <40% of normal value. Fulminant hepatitis is classified into two types; one is the acute type in which patients develop hepatic encephalopathy within 10 days, and the other is the subacute type in which hepatic encephalopathy appears between 11 days and 8 weeks.[1] The overall mortality is around 70% without liver transplantation, and the likelihood of spontaneous recovery is critical in the decision-making process.[2-4] With clinical progression of the disease, medical support alone is often unsuccessful, and liver transplantation is currently the only viable option for these patients.[2]

The severity of hepatic encephalopathy can be classified into grade (or stage) I (euphoria or depression, mild confusion, slurred speech, and disordered sleep), II (lethargy and moderate confusion), III (marked confusion, incoherent speech and sleeping but arousable), and IV (coma).[5] In the grade classification in Japan for both fulminant hepatic failure and liver cirrhosis, grade V (deep coma) are ususally differentiated from grade IV (coma) hepatic encephalopathy.[6] Patients with deep coma (grade V hepatic encephalopathy) often die from brain edema without recovery of consciousness, or they suffer from severe neurological disorders after liver transplantation.[7,8] Therefore, it is difficult for the clinician to select the appropriate patients for transplantation or, alternatively for conservative treatment.[9]

In the present report, we describe a patient with acute type fulminant

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hepatitis with deep coma (grade V hepatic encephalopathy) who was treated without liver transplantation and was rescued without any neurological deficits.

Case report

A 27-year old Japanese woman was referred to Nagasaki Municipal Medical Center, Japan, on July 1, 2003 because of highly elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. During the previous 7 days, she complained of fever (>38°C) and general malaise, and was treated with antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) at a local hospital. Medical history was negative for any liver disease and for blood transfusion. She was not a smoker, took alcohol only on rare occasions, and had no family history of liver diseases. Physical examination on admission showed grade II hepatic encephalopathy[6] and jaundice but no hepatomegaly. Laboratory data showed markedly elevated liver function tests (AST = 405 IU/L, ALT = 2,544 IU/L). Prothrombin time was 51.3 seconds (7%). Serum level of total bilirubin was 14.1 mg/dL, and serum direct/total bilirubin ratio was 0.28. Blood urea nitrogen was decreased at 2.0 mg/dL, serum ammonia was elevated at 183 μg/mL, and hepatocyte growth factor was elevated at 24.6 ng/mL (Table 1). Immunoglobulin (Ig) M antibody to hepatitis A virus (HAV), hepatitis B surface antigen (HBsAg), hepatitis B virus (HBV)-DNA, and antibody to hepatitis C virus (anti-HCV) were negative, but antibody to HBsAg (anti-HBs), antibody to hepatitis e antigen (anti-HBe), and IgM antibody to hepatitis B core antigen were positive. A drug lymphocyte stimulation test to fosfomycin calcium was weakly positive (Table 2). Abdominal ultrasonography and computed tomography (CT) showed liver atrophy but no ascites (Figure 1 a and b). The patient was diagnosed as acute type fulminant hepatitis, and was treated with plasma exchange (PE), continuous hemodiafiltration (CHDF) (10 liter/day) with polyacrylonitrile membrane, and pulse therapy of methylprednisolone (1 g/day intravenously for 3 days). However, she fell into a grade III-IV hepatic encephalopathy and was transferred to the Intensive Care Unit of Nagasaki University Hospital, Japan on July 3, 2003. Despite the above treatment, the consciousness level decreased and she fell into a deep coma (grade V hepatic encephalopathy) with mechanical ventilation on the same day. At this stage, a living donor liver transplantation (LDLT) was taken into account with a donor candidate of the patient's father according to the guideline proposed by the Acute Liver Failure Study Group of Japan.[1,10] Although cranial CT revealed no diffuse brain edema (Figure 2), electroencephalography (EEG) showed a very low voltage activity in all leads (Figure 3). Therefore, urgent LDLT was abandoned at this stage because the high risk of postsurgical neurological deficit.[7] Instead, "relative high-

Table 1. Laboratory data on admission (1)

Test	Results	Normal range
Peripheral blood		
White blood cells (/μL)	9,400	3,000-9,000
Red blood cells (×10⁴/μL)	457	350-500
Hemoglobin (g/dL)	12.1	10.0-14.0
Platelets (×10⁴/μL)	19.5	12-35
Prothrombin time (%)	7.0	70-140
Activated partial thromboplastin time (second)	67.4	25-37
Fibrinogen (mg/dL)	105	210-440
Hepaplastin test (%)	<10	70-150
Blood chemistry		
Total bilirubin (mg/dL)	14.1	0.3-1.2
Direct bilirubin (mg/dL)	4.0	0-0.3
Total protein (g/dL)	7.0	6.7-8.3
Albumin (g/dL)	4.4	4-5
Aspartate aminotransferase (IU/L)	405	13-33
Alanine aminotransferase (IU/L)	2544	8-42
Lactate dehydrogenase (IU/L)	239	119-229
Alkaline phosphatase (IU/L)	756	115-359
Leucine aminopeptidase (IU/L)	121	30-70
Gamma-glutamyl transpeptidase (IU/L)	81	10-47
Cholinesterase (IU/L)	129	203-460
Thymol turbidity test (U)	7.6	0.3-5.0
Zinc turbidity test (U)	12.6	3.2-10.9
Total cholesterol (mg/dL)	115	128-220
Amylase (IU/L)	85	50-159
Blood urea nitrogen (mg/dL)	2.0	8-22
Creatinine (mg/dL)	0.61	0.4-1.1
Ammonia (μg/mL)	183	30-86
Total bile acid (μmol/L)	37.4	<10
Hepatocyte growth factor (ng/mL)	24.6	<0.39
Alpha-fetoprotein (ng/mL)	160.9	<10
C-reactive protein (mg/dL)	0.11	<0.3

Table 2. Laboratory data on admission (2)

Test	Results	Normal range
Virus markers		
IgM antibody to hepatitis A virus (HAV)	(-)	
Hepatitis B surface antigen (HBsAg)	(-)	
Antibody to HBsAg (anti-HBs)	(+)	
Hepatitis B e antigen (HBeAg)	(-)	
Antibody to HBeAg (anti-HBe)	(+)	
Antibody to hepatitis B core antigen (anti-HBc)	(+)	
IgM antibody to hepatitis B core antigen	3.9	<0.9
Hepatitis B virus (HBV)-DNA (TMA) (LGE/mL)	<3.7	<3.7
Antibody to hepatitis C virus (anti-HCV) (COI[a])	0.44	<1.0
HCV-RNA (RT-PCR) (KIU/mL)	<0.5	<0.5
IgG antibody to hepatitis E virus (HEV)	(-)	
IgM antibody to HEV	(-)	
IgG antibody to Epstein-Barr (EB) cupsid antigen	×160	
IgM antibody to EB cupsid antigen	(-)	
IgG antibody to EB nuclear antigen	8.1	<1.0
IgM antibody to cytomegalovirus (CMV)	(-)	
IgM antibody to herpes simplex virus (HSV)	(-)	
Immunology		
Anti-nuclear antibody	(-)	
Anti-mitochondrial antibody	(-)	
DLST[b] to fosfomycin calcium (stimulation index, %)	182	≤180

[a]Cut-off index (third-generation enzyme-linked immunosorbent assay).
[b]Drug lymphocyte stimulation test.

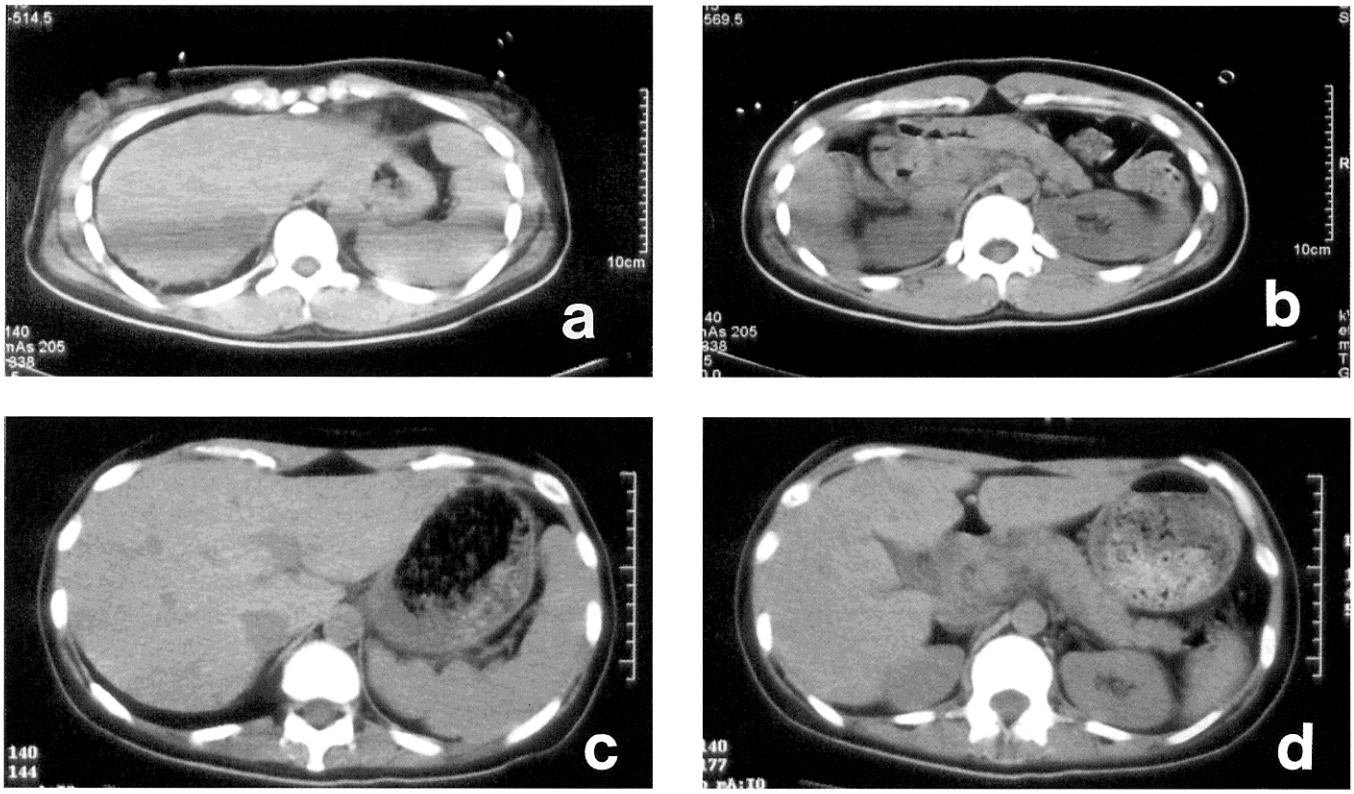

Figure 1. Abdominal computed tomography on July 3, 2003, showed liver atrophy (a, b), but liver atrophy gradually improved on September 5, 2003 (c, d).

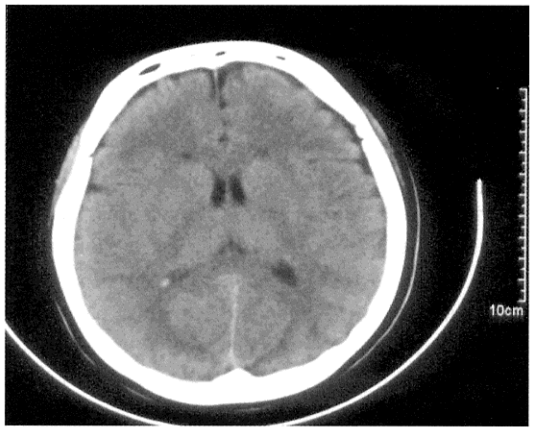

Figure 2. Cranial computed tomography on July 3, 2003, which revealed no diffuse brain edema.

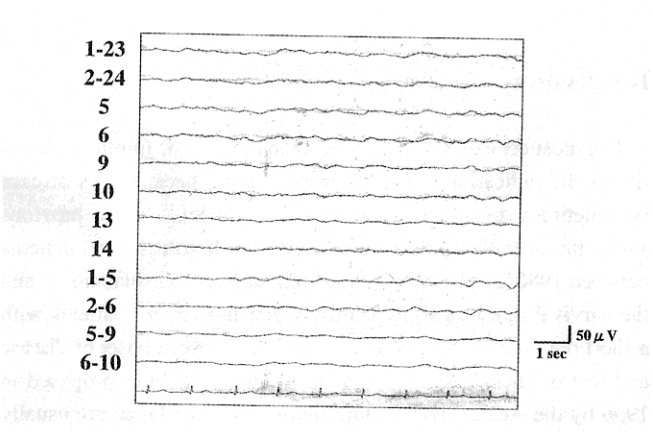

Figure 3. Electroencephalographic recording on July 4, 2003. Note the generalized low voltage in all leads.

flow" CHDF (QD+QF: 40-48 liter/day) with polymethyl methacrylate membrane was used, combined with PE, methylprednisolone, glucagon-insulin infusion, polymyxin B sulfate, and lamivudine. These treatments resulted in a gradual improvement of hepatic encephalopathy, and on July 8, hepatic encephalopathy improved to grade II without any neurological deficits, and she could be extubated. At this stage (5 days after registration), she was marked as suitable for liver transplantation (i.e. she was judged to irreversible without liver transplantation) because prothrombin time was 44%, according to the guideline proposed by the Acute Liver Failure Study Group of Japan.[1,10] However, since the encephalopathy improved to grade II or III, the above treatment was continued without liver transplantation. Prothrombin time gradually recovered to $\geq$50%, and by June 14, we were also able to discontinue the treatments of PE and CHDF. By the middle of August 2003, serum total bilirubin increased to 23.3 mg/dL, but prothrombin time improved to around 60-70%. Subsequently, liver

function tests including serum total bilirubin and liver atrophy gradually improved (Figure 1 c and d) without any complications such as infection, gastrointestinal bleeding, and renal disturbance. IgM antibody to hepatitis B core antigen returned to negative by the beginning of October 2003 (Figure 4). She remains well and at the latest follow-up in August 2004, the results of liver function tests were almost normal except for splenomegaly.

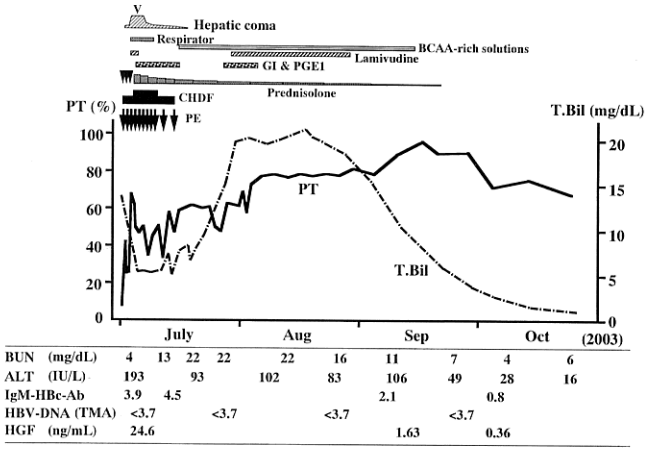

Figure 4. Clinical course. BCAA: branched-chain amino acids; GI: glucagon-insulin therapy; PGE1: prostaglandin-E1; PE: plasma exchange; CHDF: continuous hemodiafiltration; PT: prothrombin time; T.Bil: total bilirubin; BUN: blood urea nitrogen; ALT: alanine aminotransferase; IgM-HBc-Ab: IgM antibody to hepatitis B core antigen; HBV-DNA: hepatitis B virus-DNA; and HGF: hepatocyte growth factor.

Discussion

The most critical problem in the management of fulminant hepatitis is the indication of liver transplantation, because this disease is sometimes reversible without such treatment.[11] In our previous study, the overall survival rate of fulminant hepatitis in 80 patients between 1980 and 1999 was 31% without liver transplantation, and the survival rate was significantly higher in younger patients with a short pre-encephalopathy period (interval between onset of disease and that of encephalopathy).[4] In Japan, the guidelines proposed in 1996 by the Acute Liver Failure Study Group of Japan are usually used for patient selection for liver transplantation.[1,10] The criteria consist of the following five conditions: (1) Age $\geq$ 45 years; (2) Interval between onset of disease and that of encephalopathy $\geq$ 11 days; (3) Prothrombin time <10%; (4) Serum total bilirubin $\geq$ 18 mg/dL; and (5) Serum direct/total bilirubin ratio $\leq$ 0.67. When the patient fulfills two or more of these five conditions, the patient is registered as a candidate for liver transplantation. Because there are some survivors among these patients after intensive therapy without liver transplantation, reconfirmation 5 days after registration is recommended for such patients. At that time, the patient could be marked as unsuitable for liver transplantation if prothrombin time recovers to $\geq$ 50%, and also the encephalopathy improves to grade 0 or I, or improves its grade by two or more. The overall predictive accuracy of this guideline was 82% in a prospective study of 190 patients in 43 hospitals in Japan.[3] However, Fujiwara et al.[1] reported that the predictive accuracy of this guideline was 90% for the subacute type fulminant hepatitis, but less than 80% for the acute type. Therefore, they concluded that the practical usefulness of the guideline seemed to be limited in the subacute type.[1] The clinical outcome of our patient was in line with this finding: the above guidelines indicated that the acute type fulminant hepatitis in our patient was irreversible without liver transplantation 5 days after registration, but she finally showed recovery without such treatment.

It is often difficult to predict the reversibility of brain damage in patients with deep coma (grade V hepatic encephalopathy) before liver transplantation in acute hepatic failure.[12] Hattori et al.[13] reported that the best predictive factor for post-transplantation neurological deficit was brain edema on cranial CT rather than coma grade or EEG results. Indeed, Kobayashi et al.[10] reported a case of complete recovery (without any neurological disorders) from fulminant hepatic failure with grade V hepatic encephalopathy and almost flat waves on EEG but no severe brain edema following liver transplantation. Kubota et al.[8] proposed two mechanisms for deep hepatic coma; brain edema and elevated blood concentrations of toxins including ammonia and aromatic amino acids. Therefore, patients with severe (diffuse) brain edema should be considered unsuitable for liver transplantation, while patients without brain edema should not be completely excluded from liver transplantation candidates even if they have low-voltage or flat EEG.[7] However, the indications for liver transplantation in patients with deep coma (grade V hepatic encephalopathy) are still controversial because the reversibility of severe coma cannot be accurately predicted before the transplantation.[14,15] Prolonged deep hepatic coma without severe brain edema in our patient might be, at least in part, attributed to the sedative state in mechanical ventilation. However, Matsubara et al.[16] reported that prolonged hepatic coma was often seen in cases with acute type fulminant hepatitis B for unknown reason.

Our patient was treated with lamivudine because fulminant hepatic failure might be due to HBV infection rather than drug (fosfomycin calcium)-induced hepatitis, although the route of transmission was not known. The reason for this expectation is that IgM antibody to hepatitis B core antigen was positive at the initial presentation and it became negative approximately three months later, although HBsAg and HBV-DNA were negative and anti-HBs was already positive at the initial presentation. In patients with fulminant hepatitis B, rapid clearance of HBsAg and enhanced anti-HBs antibody production have been observed, and as in the present case, HBsAg has often been cleared by the time of initial presentation.[17] In such cases, the presence of IgM antibody to hepatitis B core antigen is the only diagnostic marker of acute HBV infection.[18] The prognosis of those who exhibit anti-HBs only is no better than those with HBsAg alone,[17] but the efficacy of lamivudine in the present case was obscure because HBV-DNA was already negative at the initial presentation.

In the present case, recovery from fulminant hepatic failure and

prolonged deep coma without liver transplantation could attribute to the following factors:. (1) The patient was suffered from "acute type" fulminant hepatitis, and prothrombin time was improved promptly after treatment; (2) The "relative high-flow" CHDF was used (QD+QF: 40-48 liters/day);[8] and (3) Lack of any complication such as brain edema, infection, renal failure, and gastrointestinal bleeding throughout the clinical course. A more accurate guideline for early prediction of poor recovery will be needed for proper therapeutic management of fulminant hepatic failure by early identification of those patients who need liver transplantation.[9]

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